IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/989,674
Applicant	:	Gordon Woods
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Director of the United States Patent
and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. §1.132

I, Gordon L. Woods, declare that:

1. I am the same Gordon L. Woods identified as the applicant of the above-referenced patent application.

2. I received a B.S. degree from the University of Idaho in 1978 and a D.V.M. in 1978 from Colorado State University. I further received a M.S. in veterinary science in 1982 and a Ph.D. the following year from the University of Wisconsin. From 1983-1986 I was an Instructor and then an Assistant Professor at the New York State College of Veterinary Medicine in Ithaca, New York. From 1986-1988 I was an Associate Professor in the Department of Veterinary Clinical Medicine and surgery at Washington State University in Pullman, Washington. From 1988 to the present I have been a Professor at the University of Idaho, initially a Professor in Veterinary Science and currently a

Professor in Animal and Veterinary Science. For the past seven years, I also have been the President of CancEr2, Inc. A copy of my C.V. is attached hereto as Exhibit 1.

3. I have read and understand the rejections of the pending claims of the above-referenced application set forth in the outstanding Office Action of September 24, 2004. In that Action, the examiner rejected all of the pending claims under 35 U.S.C. §112, first paragraph, on the basis that the full scope of the claims is not enabled by the specification. More specifically, the examiner has asserted that although the specification is enabling for the specific low range of cadmium to be administered to a human by the particular route employed, the specification does not provide reasonable enablement for the full dose range of about 0.025 - 2 mg/day to be administered to a human by any route of administration in view of cadmium's known toxicity.

4. Cadmium has long been considered a nonessential element which can, indeed, be toxic to humans when administered in certain doses. As described in detail in my application, however, I have discovered that when administered in certain doses cadmium is not toxic, and, in fact, that humans can suffer from a cadmium deficiency, with adverse consequences, which can be treated through the administration of cadmium.

The examiner has asserted that the specification fails to provide sufficient information that would allow one of skill in the art to fully practice the invention without undue experimentation. The specification teaches daily dosage amounts and routes of administration and thus has provided guidance on how to use the invention. With regard to the examiner's concerns regarding toxicity, the application includes an example in which 1 mg of a cadmium salt was orally administered daily to a group of men for a six week period with no toxic effects. The application teaches the administration of cadmium in an oral dose as high as 2 mg per day, and a further experiment detailed below illustrates that this dose can be administered safely with no toxic effects to the patient.

5. A daily oral dose of 2 mg of cadmium sulfate was administered to a healthy human male over a nine week period. The cadmium sulfate was administered every morning, one hour prior to any food intake. Blood and urine samples were collected from the man one day prior to the beginning of treatment (considered day 1 of the study) and then on days 20, 34, 48, 62 and 73. The cadmium sulfate was administered daily on days 2 - 64 of the study period. In order to standardize body chemicals prior to sample collection, the man food fasted for 24 hours each day that the blood and urine were collected, beginning at 6:00

p.m. the evening before the sample collections and continuing until 6:00 p.m. the evening of the collection day. Samples were collected between 10:00 a.m. and 3:00 p.m. Two liters of bottled water were provided to the man to drink freely throughout the sample collection day. Complete urinalysis, comprehensive metabolic, urine protein and hemogram tests were preformed on the blood and urine samples.

No evidence of toxicity was detected throughout the nine week cadmium treatment protocol. Protein in the urine is a symptom of cadmium toxicity. Trace protein was detected in the man's urine on days 20 and 34 of the protocol, but no protein was detected on days 48, 62 and 73. As a result, the trace protein detected on days 20 and 34 was interpreted as incidental and not to have been caused by the cadmium administration.

This protocol illustrates that 2 mg of a cadmium salt can be safely administered for an extended period to humans.

6. In addition to the claims of my application directed to the oral administration of cadmium in a dosage range of about 0.5 to about 2 mg per day, there also are claims directed to the parenteral administration of a cadmium salt in a dosage range of about 0.025 to about 0.1 mg per day. When cadmium is administered orally, approximately 95% of the cadmium will pass through the gastro-intestinal tract and not be absorbed into the

blood, tissue or other organs. *WHO Food Additives Series #24*, p.166 (1989), citing Kitamura, 1972; Rahola et al., 1972; Yamagata et al., 1974; Flanagan et al., 1978; and Shaikh and Smith, 1980. Thus, only about 5% of the cadmium administered orally is available in the body as a therapeutic agent. In contrast, when cadmium is administered parenterally, it is systemically absorbed. Accordingly, only about 5% of the amount administered orally is necessary for parenteral administration to achieve comparable results. Thus, as suitable oral dosages are within the range of about 0.5 mg to about 2 mg per day, suitable parenteral doses are within the range of about 0.025 to about 0.1 mg per day.

7. Further evidence that cadmium administration at the doses provided in my application are not toxic and will serve to treat a cadmium deficiency can be extrapolated from "Toxicological Evaluation of Certain Food Additives and Contaminants," prepared by the 33rd Meeting of the JOINT FAO/WHO Expert Committee on Food Additives and published in 1989 in the *WHO Food Additives Series #24*, pp 182-219. A copy of this paper is attached hereto as Exhibit 2.

This paper reports on toxicity studies in which cadmium salts were orally administered to male rhesus monkeys in varying dosages and over different periods of time. Rhesus monkeys are a

good model for humans because humans and rhesus monkeys metabolize cadmium similarly. Nomiyama et al., *Environ. Health Perspect.* 28:223-243 (1979). In reviewing the FAO/WHO report, I have assumed an average weight for the monkeys of 12.5 kg. If one also assumes an average weight for human males of 70 kg, the per weight conversion factor is 5.6 to determine the comparable amounts of cadmium that could be administered to humans to achieve similar results. In the first study reported, each monkey was given 0.1, 0.3, 3.0 or 30.0 mg of cadmium salt per day (100 g of food containing 1, 3, 30 or 300 mg/kg, respectively); the equivalent dose of cadmium per human would have been 0.56, 1.68, 16.8 and 168 mg cadmium/day. The study continued for 24 weeks. No toxicity was shown for monkeys who received the lowest dose, equivalent to humans receiving 0.56 mg/day. Toxicity was shown in monkeys receiving the highest dose, which significantly exceeds the maximum dose taught in my patent application; no report was provided regarding the intermediate doses.

In a second study, for one month groups of monkeys received 0, 0.3, 1.0, 3.0 or 10.0 mg cadmium/day (100 g of food containing 0, 3, 10, 30 or 100 mg/kg, respectively), equivalent to adult humans receiving 0, 1.68, 5.6, 16.8 or 56 mg cadmium/day, then for 13 months were administered 0, 0.45, 1.5, 4.5 or 15.0 mg cadmium/day, respectively, equivalent to 0, 2.52, 8.4, 25.2 or

84.0 mg cadmium/day for adult humans. For the following 16 months, the monkeys received 0, 0.6, 2.0, 6.0 or 20.0 mg cadmium/day, respectively, equivalent to 0, 3.36, 11.2, 33.6 or 112.0 mg cadmium/day for adult humans. The paper reports that no adverse effects were recorded for the monkeys who received 3 mg/kg food/day (the human equivalent of 1.68 mg/day for one month, 2.52. mg/day for the next 13 months and 3.36 mg/day for the following 16 month) and in the 10 mg/kg food/day group (the human equivalent of 5.6 mg/day for one month, 8.4 mg/day for the next 13 months and 11.2 mg/day for the next 16 months) "slight pathological changes were observed in the tubular epithelium during the 101st week but no other adverse effect were noted." These results indicate that the maximum doses advocated in my application would be safe and non-toxic.

In a third study, rhesus monkeys received a cadmium salt at a level of 3 mg/kg food (the human equivalent of 1.68 mg/day) for one year, with some receiving a dose of up to 30 mg/kg food (the human equivalent of 16.8 mg/day) for a further two years. The authors report that after 3 years, no proteinuria or abnormalities in creatinine clearance were noted. Again, these results indicate that the maximum doses set forth in my application for human administration are safe and non-toxic.

The paper further reports the results of a long-term study that continued for up to 9 years, in which rhesus monkeys received 200g of feed/day to which were added a cadmium salt at a concentration of 0, 3, 10 , 30 or 100 mg. The monkeys thus received 0, 0.6, 2.0, 6.0 or 20.0 mg cadmium/day, respectively, which if administered to humans would be 0, 3.36, 11.2, 33.6 or 112 mg/day, respectively. The authors report that no renal function abnormality was seen in the 3 or 10 mg/kg dose groups (3.36 mg/day/human equivalent or 11.2 mg/day/human equivalent). No pathological changes in the kidneys were noted for the 3 mg/kg group; mild lesions were observed in the 10 mg/kg group. These results also indicate that the maximum dose recommended in my application is nontoxic in humans.

8. The results provided in the FAO/WHO study and from my own studies indicate that the cadmium doses for humans set forth in my application are non-toxic and can be administered safely.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Gordon L. Woods

Gordon L. Woods

24 March 2005

Date